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EXAMINER	
KOSAR, AARON J	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,194	BORDONI ET AL.	
	Examiner	Art Unit	
	AARON J. KOSAR	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-60* is/are pending in the application.

4a) Of the above claim(s) *47-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-46 and 53-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/10/06;12/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claim 31-46 and 53-60 (composition, first method of making the composition, first method of using the composition, and kit comprising the composition), in the reply filed on November 19, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without** traverse (MPEP § 818.03(a)).

Claims 31-60 are pending. Claims 47-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 31-46 and 53-60 are pending *and* have been examined on their merits to the extent the claims are drawn to the elected invention.

The election/restriction requirement is still deemed proper and therefore made FINAL..

Information Disclosure Statement

The information disclosure statements (IDS) submitted on February 10, 2006 and December 13, 2006 have been considered by the examiner. Several references listed therein appear to be the Abstracts obtained from electronic databases. These references have been lined through on the IDS and relisted on a PTO-892 to correct bibliographic information which was omitted from the IDS.

Claim Objections

Claims 31-46 and 53-60 are objected to because of the following informalities:

The claims lack articles which distinguishing the correlation of independent claims and the dependent claims. To avoid any potential issues which may arise as a result of the omitted

articles as to whether the claims are dependent or merely exemplary, the independent claims should be amended to recite, for example, "A culture medium..", "A process..", and "A method.." (and "A kit..") with the correlated dependent claims amended to recite, for example, "The culture medium of claim 31..", "The process of claim 42..", and "The method of claim 53..", respectively.

The phrase "characterized for further comprising" in claim 37 appears to be an inadvertent representation of the phrase "further comprising".

The phrases "in form of" and "a lyophilized" in claim 40 are objected to, because the claims appear to inadvertently omit the article "the" from the phrase "in the form of" and omitting the implicit term "medium" from the phrase "a lyophilized medium" (*c.f.* page 7,¶ 2).

Claim 53 appears to inadvertently recite typographical variants/errors of the phrase "growing, expanding, maintaining, and/or differentiating..".

Claim 60 is objected to for not ending in a period. MPEP § 804.01(m) states that, "Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations. See *Fressola v. Manbeck*, 36 USPQ2d 1211 (D.D.C. 1995)."

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd ¶

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-46 and 53-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31-46 and 53-60 are indefinite, because the phrase "medium conditioned by cytokines and soluble factors by immortalized untransformed hepatocytes that are differentiated, polarized epithelial cells" is unclear. The phrase is unclear, because "conditioning" is defined in the specification as a cell-based excretion process (conditioning with cells), and thus it appears that claimed "conditioning by cytokines and soluble factors" (conditioning with excretions) is inconsistent with the specified/disclosed definition of conditioning. Additionally, it is unclear what components are introduced into the medium, if any, by conditioning.

The term "cytokine" in claims 37-39 is unclear, because claim 31 recites a composition *conditioned by* cytokine, but it is unclear if the composition *comprises* a cytokine. To the extent claim 31 may require the presence of a cytokine, it is further unclear if the cytokine recited in claims 37-39 are the cytokine of claim 31 or if the cytokines are separate cytokines unrelated to the cytokine of claim 31.

Additionally, the specification recites the "soluble factors..include.. cytokines"; however, the claims recite a composition conditioned by "cytokines and soluble factors"(claim 31; specification, pg.1, last ¶). It is unclear if the phrase "cytokines and soluble factors" is a singular, collective component (e.g embraced by "cytokines") or if the phrase refers to multiple components (e.g. embraced by cytokines and soluble factors excluding cytokine or by a first cytokine and a soluble factor comprising a second cytokine which is different from the first cytokine).

Each interpretation is a broad and reasonable interpretation of the claims; however, each embraces a different subject matter. Thus one would not be apprised as to the subject matter

Applicant intends to embrace by the claims and one would not be apprised as to the metes and bounds of the claims, thereby rendering the claims indefinite.

Claims 42-46 are rejected because the term "culture medium" in claim 42 is recited as both the product (method of making a culture medium) and as a reagent ("in a cell culture medium") used to make the product culture medium. Furthermore, the term "culture medium" in claim 44 is unclear, because claims 42 recites the term twice and it is unclear to which "culture medium" of claim 42, the term recited in claim 44 is drawn.

Claim 44 contains the culture media trademarks/trade names, including the tradenames: RPMI, RPMI-1640, HAM'S F12, ISOCOVE'S, MCCOY'S, and DULBECCO'S MODIFIED EAGLES MEDIUM (DMEM).

Since a trademark or trade name is used to identify a source of goods, and not the goods themselves, where possible, to clearly and unambiguously describe the trademarked material, where a claim recites a trademark/trade name in a claim, the trademark/trade name should minimally be capitalized wherever it appears and in the first recitation in the specification and claims unabridged or unabbreviated (e.g. ROSWELL PARK MEMORIAL INSTITUTE (RPMI); MODIFIED EAGLES MEDIUM (MEM): ISOCOVE'S MEME (IMEM), MCCOY'S MEM (MMEM).

Also, a trademark should further include the appropriate ™ or ® symbol; and, to the extent possible, should be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Regarding claim 60, the word "means" is preceded by the word(s) "laboratory" in an attempt to use a "means" clause to recite a claim element as a means for performing a specified function. However, since no function is specified by the word(s) preceding "means," it is impossible to determine the equivalents of the element, as required by 35 U.S.C. 112, sixth paragraph. See *Ex parte Klumb*, 159 USPQ 694 (Bd. App. 1967).

Claims 31-46 and 53-60 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01.

The omitted elements are the minimally required chemical components provided in the composition. At a point of novelty, Applicant fails to set forth the criteria that define a "culture medium conditioned by cytokines and soluble factors", other than providing a functional definition of the components (i.e. culture medium, cytokines, and soluble factors) as being "released by..hepatocytes" and said medium as "free from conditioning cells, when used". Such functional language describes nothing about the chemical, physical or structural properties of the compounds present in the composition or the use of said compounds in the related methods. Attention is directed to *General Electric Company v. Wabash Appliance Corporation* 37 USPQ 466 (US 1938), at 469, speaking to functional language at the point of novelty as herein employed.: "the vice of a functional claim exists not only when a claim is 'wholly" functional, if that is ever true, but when the inventor is painstaking when he recites what has already been seen, and then uses conveniently functional language at the exact point of novelty". Functional language at the point of novelty is further admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC 1997) at 1406: stating this usage does "little more than outline goals appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". Claims employing functional language at the point of novelty neither provide those elements required to practice the invention, nor "inform the public during the life of the patent of the limits of the monopoly asserted.", *General Electric Co. v. Wabash Appliance Corp.*, at 468.

The term "free from conditioning cells, when used" in claim 31 is a relative term which renders the claim indefinite. The term "free from" is a relative term, because while the claim provides an object of "conditioning cells" from which the "culture medium" is made "free", it is unclear what extent of freedom or what manipulations are required by the claim for a culture medium to be *free from* conditioning cells. One may reasonably interpret degrees of "freed from" as possibly including: absolute removal of conditioning cells (e.g. filtration), partitioning (e.g. sedimenting, precipitating, centrifuging, or pelleting), mere molecular separation or conditioning-cell deactivation (deaggregating/dissociating/irradiating of media from conditioning cells), or gradations/ranges thereof. Also the term "when used" further blurs the metes and bounds of what components and what degree of contact (status of "free from") is actually required by the claims. The term "free from" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of "free from", and one of ordinary skill in the art would not be reasonably apprised of he scope of the invention, thereby rendering the claims indefinite.

The phrase "further characterized for being depleted for at least one biological molecule.." in claim 38 contains the relative term "depleted" which renders the claim indefinite. The term is indefinite, because it is unclear what amounts are embraced by a state of depletion. The term "depleted" is not defined by the claim, the specification does not provide a reference point and/or standard for ascertaining the requisite degree of "depleting", and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention, thereby rendering the claims indefinite.

The term "separating..before the use" in claim 42 is a relative term which renders the claim indefinite. The terms "separating" and before are relative terms, because while the claim provides an object of "hepatocytes" which are separated and steps comprising incubating and separating, it is unclear what from what component(s)/object(s) the hepatocytes are separated. It is also unclear what step is defined by "the use" in order for the method to be practiced "before" said use. The terms "separating" and "before the use" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of "separating" or sequence of steps by which "before" may be determined, and one of ordinary skill in the art would not be reasonably apprised of he scope of the invention, thereby rendering the claims indefinite.

In claim 46, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 46 recites the terms "such as" and "like", the broad recitation of *solid/semisolid/gels*, and the claim also

recites *plastic/gels/collagen,..agar* which are the narrower statements of their respective range/limitation.

Claims 33 recites the limitation "said MMH cells". There is insufficient antecedent basis for this limitation in the claim, because claim 32, but not claim 31, recites MMH cells.

Claims 34 and 35 recite the limitation "said cultured mammalian cells". There is insufficient antecedent basis for this limitation in the claim, because claim 31 does not recite a cultured mammalian cell.

Claims 35 and 55 recite the limitation "non-human embryonic/embryonal stem cells". Additionally, claims 34, 36, 54, and 56-59 recite the terms including "cord-blood stem cells", "endodermal", "ectodermal", "mesodermal", "adult progenitor", "stem cells", "NK", "dendritic cells", and "endothelial cells". There is insufficient antecedent basis for this limitation in the claims, because claims 31/53 recite "adult mammalian cells", but do not recite embryonic cells, etc. and it is unclear from the disclosure if "adult mammalian cells embraces" each of the above terms/species of cells.

Claim 31 provides for a culture medium "when used", but, since the claim does not set forth what method/process applicant is intending to encompass by a "use" *per se* or the minimal required "use" method/process steps, the claims are rendered indefinite. A claim is indefinite where it merely recites a use without any objects embraced by "when used" and/or active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 112, 1st ¶

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-46 and 53-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is noted that with respect to the biological materials (i.e. cell lines and genetically modified cell lines) required to practice the claimed invention, it is unclear if said materials are (I) currently available from repository, commercial sources, or *via* methods known in the art *or* if the said materials are (II) not so available/obtainable.

(I) Where the biological materials appear to be or are established to be available, then it should also appear that these materials should remain available to the public beyond the effective life of the patent. Any information to the contrary which comes to Applicant's attention *during the prosecution of this application*, must be entered in the record or otherwise be brought to the attention of the Office by the applicant.

> *If an Applicant has adequately established that a biological material is known and readily available, the Office will accept that showing. In those instances, however, the Applicant takes the risk that the material may cease to be known and readily available. Such a defect cannot be cured by reissue after the grant of a patent.* (MPEP 2404.01)

(II) If the biological material is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of a requisite

immortalized untransformed hepatocyte cell line(s) or genetically-modified hepatocyte cell line(s) thereof (e.g. MMH and HuH7 cell lines). See 37 CFR 1.802.

To the extent the specification does not provide a repeatable method for obtaining said hepatocytes, including MMH or HuH7 or other cell lines, and it does not appear that the materials are readily available materials, then deposit of each of the required cell line(s) would satisfy the enablement requirements of 35 U.S.C. 112, see 37 CFR 1.801- 37 CFR 1.809.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination, or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-41 are rejected under 35 U.S.C. 102(b) as being anticipated by WILEY (US 6,284,236)

The claims are generally drawn to a composition comprising a culture media.

WILEY anticipates the claims by teaching a cell culturing media, wherein "media was replaced with DMEM and cytokines" (example 11, column 41).

Claims 31-46 and 53-60 are rejected under 35 U.S.C. 102(b) as being anticipated by AIUTI (PTO-1449, 2/10/2006).

AIUTI anticipates the claims by teaching a medium composition comprising cytokines/soluble factors. Aiuti also teaches MMH-coculture medium (MMH present) and MMH-conditioned medium (MMH-depleted) used to contact ("culture") hematopoietic medium and the use of collagen-coated plates (e.g. page 1646 left column, materials and methods, ¶3-4; page 1653, ¶1). Aiuti also teaches incubating/culturing for 7-9 days colonies of cells in an assay media, the assay media comprising:

"..in 1 mL of methylcellulose assay medium consisting of 1% methylcellulose in IMDM supplemented with 20% fetal calf serum, 1% bovine serum albumin (Sigma Chemical Co., Milan, Italy), 10-4 mol/L 2-mercaptoethanol, 1% penicillin-streptomycin, 1% L-glutamine, 2 U/mL recombinant human erythropoietin (EPO) (Amgen, Milan, Italy), 10% X-63-IL-3 conditioned medium,13 5% TSA–granulocyte-macrophage colony–stimulating factor (GM-CSF)-conditioned medium,14 10 ng/mL granulocyte colony–stimulating factor (G-CSF) (Schering-Plough, Milan, Italy), and 10 ng/mL mouse stem cell factor (SCF) (Boehringer-Mannheim, Monza, Italy)."(page 1646).

Aiuti also teaches coculturing a MMH conditioned cell culture media with recipient progenitor cells ("hematopoietic cells")(pg.1646, ¶ 4-5) and that MMH cells exhibit a pattern of cytokine expression (pg.1646, ¶1; page 1647, results, ¶3). Auiti teaches that *long-term* maintenance in the absence of a feeder layer (i.e. media unconditioned by MMH cell lines) is depleted/exhausted after 1 week (page 1647, right column, ¶2); that the "expression of .. cytokines is consistent with the capacity of MMH lines to induce proliferation and maturation.."; and that "non-transformed, polarized hepatocytes in culture are capable of expressing hematopoietic cytokines normally produced in vivo by hepatocytes", including for example IL-6 and GM-CSF (Page 1649, discussion, ¶3—page 1652, ¶1). Auiti also beneficially teaches that direct cell-cell contact is required for long-term (e.g. ≥weeks) maintenance of cells, but that MMH-conditioned media (i.e. in this context, a cell-free conditioned media to which hematopoietic cells are applied) to a lesser extent supports culturing and differentiation of hematopoietic cells, though not long-term maintenance (page 1653, ¶1). Taken together, Aiuti further constitutes a teaching of the range of media comprising: unconditioned media (no MMH), MMH-conditioned media (spent media/MMH-removed), and MMH-supplemented media (MMH-cocultured).

To the extent that WILEY or AIUTI ("Wiley/Aiuti") may be silent or may differ from the instant claims regarding the origin or source of the cytokine/soluble factor or an intended use, because Wiley/Aiuti recite the minimal chemical composition required by the claims and also recite a conditioning with and/or presence of cytokines/soluble factors in the composition, the chemical species (e.g. erythropoietin (EPO), Il-6, etc.), are deemed to be identical on the chemical level and inseparable from their properties irrespective of the source of the chemical species, especially in the absence of objective evidence to the contrary and the criticality of a particular chemical source.

Please note, since the Office does not have the facilities for examining and comparing Applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. *See In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980), and "as a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

Claims 31-39, and 42-46 are rejected under 35 U.S.C. 102(b) as being anticipated by MULLIGAN (US 5,521,076 A) and as evidenced by BECTON-DICKINSON (BD BIOSCIENCES, "BD PRIMARIA™ Cultureware", Becton, Dickinson, and Company, <https://www.bdis.com/discovery_labware/ products/display_product.php?keyID=193>, 2007 (accessed online 4/16/2008), 2 pages.

MULLIGAN anticipates the claims by teaching culturing a PRIMARIA™ plate of hepatocytes in culture media, including DULBECCO'S MINIMAL ESSENTIAL MEDIA (DMEM). As evidenced by BECTON-DICKINSON, PRIMARIA™ comprises a solid plastic/modified polystyrene surface (BD, page 1, ¶5 and figure spanning page 2; see also MULLIGAN, Example 1, column 16).

Mulligan also teaches filtering the conditioned media to remove detached cells and to obtain a spent media. Mulligan further teaches treating a subconfluent plate of hepatocytes (recipient hepatocytes) by the removal the media and replacing said media with the spent media (column 13, ¶2-3).

Since the spent media is taught to be recycled to support an intended use in subsequent recipient hepatocyte growth cycles (and directed also to an additional intended use of viral transfection), the hepatocytes by the process of culturing would be expected to have intrinsically conditioned the spent media with cytokines and soluble factors. Additionally, to the extent the hepatocyte cell of Mulligan may differ from the instant immortalized hepatocyte in that the hepatocyte of Mulligan may not be not a genetically modified hepatocyte cell (e.g. MMH), said modified cell would be expected to be inseparable from and embraced by its function as a hepatocyte and thus still anticipated by Mulligan, especially in the absence of objective evidence to contrary or evidence to the criticality of some undisclosed property (e.g a specific genetic modification of MMH cells not present in the unmodified hepatocyte) which distinguished the product composition (i.e.the culture media or cell-free culture media) from media from naturally-occurring hepatocytes, including that of Mulligan.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31-46 and 53-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over AIUTI (PTO-1449, 2/10/2006) under 35 U.S.C. 102(b) above as anticipated by AIUTI or, in the alternative, under 35 U.S.C. 103(a) as obvious over AIUTI in view of NAUGHTON (US 7,118,746 B1).

The claims are drawn as presented above.

The teachings of AIUTI are above.

The instant claims differ from Aiuti in that Aiuti is silent regarding the explicit/ enumerated teaching of the myriad of possible component combinations (hematopoietic cells, organismal origin of said cells, form, culture media), mode of separation, or reaction times embraced by the claims.

It would have been obvious to prepare the conditioned medium in a different form, with other natural/modified (hematopoietic) cells, including of other origin, in other culture media, or

using various modes of separation, because NAUGHTON teaches that the claimed alternatives are known for the purpose of conditioned media.

One would have been motivated to modify the media for the combinations, because Naughton teaches:

> *"conditioned media..may be comprised of any known defined or undefined medium and may be conditioned using any eukaryotic cell type. The medium may be conditioned by stromal cells, parenchymal cells, mesenchymal stem cells, liver reserve cells, neural stem cells, pancreatic stem cells and/or embryonic stem cells. Additionally, the cells may be genetically modified. A three-dimensional tissue construct is preferred. Once the cell medium..is conditioned, it may be used in any state. Physical embodiments of the conditioned medium include, but are not limited to, liquid or solid, frozen, lyophilized or dried into a powder"*(Abstract; see also column 4, ¶4 through column 5, ¶ 2).

Naughton also teaches that cells can be conditioned by cells, including liver, liver reserve cells, adult/fetal cells, etc., "cultured in monolayer, beads, or three dimensions by any means", (§ 5.2.1), and can be genetically modified to produce IL-6, etc. (§5.5); that "commercially available media such as RPMI 1604,..ISOCOVE'S, MCCOY'S" may be used (§5.3, column 14, last ¶); and that whole cells and cellular debris may be processed to remove cells and cellular debris (§5.4, column 17, ¶1, last sentence). Naughton further teaches that culture media may be harvested and then further processed by filtration including filtering with 10,000MW cut-off AMICON filters (§5.6, column 21,¶1, last sentence;§5.7 column 22, ¶1-2) and, when using or in the presence of collagen, removal of collagen by centrifugation (column 23, ¶1).

Naughton still further teaches a method of using the conditioned medium in that the conditioned media has been shown to induce proliferation of cells, including fibroblasts and keratinocytes (column 25, ¶2). This constitutes an implicit teaching minimally requiring the contacting of media with the cells.

To the extent the composition and methods may differ by a reaction/contact time, and since Aiuti and Naughton generally teach incubating/culturing conditions and/or times, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. reaction (contact/incubating) times), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP § 2145.05).

One would have had a reasonable expectation of success in making or using the composition as claimed, because the success of the composition/methods merely requires the contacting of the components.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of objective evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AARON J. KOSAR whose telephone number is (571)270-3054. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday,EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Examiner, Art Unit 1651

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